Section 21.7 showed that all carboxylic acid derivatives hydrolyze to carboxylic acids. Water and hydroxide ion, the nucleophiles involved in hydrolysis, are only two of the nucleophiles that react with carboxylic acid derivatives. This section shows how the reactions of other nucleophiles with carboxylic acid derivatives can be used to prepare other carboxylic acid derivatives. As you proceed through this section, notice how all of the reactions fit the pattern of nucleophilic acyl substitution.

### A. Reactions of Acid Chlorides with Nucleophiles

Among the most useful ways of preparing carboxylic acid derivatives are the reactions of acid chlorides with various nucleophiles. Because of the great reactivity of acid chlorides, such reactions are typically very rapid and can be carried out under mild conditions. Recall that acid chlorides are readily prepared from the corresponding carboxylic acids (Sec. 20.9A).

**Reactions of Acid Chlorides with Ammonia and Amines** Acid chlorides react rapidly and irreversibly with ammonia or amines to give amides. Reaction of an acid chloride with ammonia yields a primary amide:

\[
\text{CH}_3\text{(CH}_2\text{)}_8\text{C}=-\text{Cl} + 2\text{NH}_3 \longrightarrow \text{CH}_3\text{(CH}_2\text{)}_8\text{C}=\text{NH}_2 + \text{NH}_4\text{Cl}^- \quad (21.31)
\]

Reaction of an acid chloride with a primary amine (an amine of the form RNH₂) gives a secondary amide:

\[
\text{Ph}=-\text{C}=\text{Cl} + \text{PhCH}_2\text{CH}_2\text{NH}_2 \longrightarrow \text{Ph}=-\text{C}=\text{NHCH}_2\text{CH}_2\text{Ph} + \text{HCl}^- \quad (21.32)
\]

Reaction of an acid chloride with a secondary amine (an amine of the form R₂NH) gives a tertiary amide:

\[
\text{Ph}=-\text{C}=\text{Cl} + \text{H}_2\text{N}:+ \text{NaOH} \longrightarrow \text{Ph}=-\text{C}=\text{N}: + \text{H}_2\text{O} + \text{Na}^+\text{Cl}^- \quad (21.33)
\]

These reactions are all additional examples of nucleophilic acyl substitution.
21.8 REACTIONS OF CARBOXYLIC ACID DERIVATIVES WITH NUCLEOPHILES

A proton is removed from the amide nitrogen in the last step of the mechanism. Unless another base is added to the reaction mixture, the starting amine acts as the base in this step. Hence, for each equivalent of amide that is formed, an equivalent of amine is protonated. When the amine is protonated, its electron pair is taken “out of action,” and the amine is no longer nucleophilic.

Hence, if the only base present is the amine nucleophile (for example, as in Eq. 21.3), then at least two equivalents must be used: one equivalent as the nucleophile and one as the base in the final proton-transfer step.

The use of excess amine is practical when the amine is cheap and readily available. Another alternative is to use a tertiary amine (an amine of the form \( R_3N \)) such as triethylamine or pyridine as the base (Eq. 21.32).

The presence of a tertiary amine does not interfere with amide formation by another amine because a tertiary amine itself cannot form an amide. (Why?) The use of a tertiary amine is particularly practical if the amine used to form the amide is expensive and cannot be used in excess.

Yet another alternative for amide formation is to use the Schotten–Baumann technique. In this method, the reaction is run with an acid chloride in a separate layer (either alone or in a solvent) over an aqueous solution of NaOH (Eq. 21.33). Hydrolysis of the acid chloride by NaOH is avoided because acid chlorides are typically insoluble in water and therefore are not in direct contact with the water-soluble hydroxide ion. The amine, which is soluble in the acid chloride solution, reacts to yield an amide. The aqueous NaOH extracts and neutralizes the protonated amine that is formed.

Further Exploration 21.3
Reaction of Tertiary Amines with Acid Chlorides
The important point about all of the methods for preparing amides is that either two equivalents of amine must be used, or an equivalent of base must be added to effect the final neutralization.

**Reaction of Acid Chlorides with Alcohols and Phenols**

Esters are formed rapidly when acid chlorides react with alcohols or phenols. In principle, the HCl liberated in the reaction need not be neutralized because alcohols and phenols are not basic enough to be extensively protonated by the acid. However, some esters (such as tert-butyl esters; see Further Exploration 21.2) and alcohols (such as tertiary alcohols; Secs. 10.1 and 10.2) are sensitive to acid. In practice, a tertiary amine like pyridine is added to the reaction mixture or is even used as the solvent to neutralize the HCl.

As these examples illustrate, esters of tertiary alcohols and phenols, which cannot be prepared by acid-catalyzed esterification, can be prepared by this method.

Sulfonate esters (esters of sulfonic acids) are prepared by the analogous reactions of sulfonyl chlorides (the acid chlorides of sulfonic acids) with alcohols. This reaction was introduced in Sec. 10.3A.
**Reaction of Acid Chlorides with Carboxylate Salts**

Even though carboxylate salts are weak nucleophiles, acid chlorides are reactive enough to react with carboxylate salts to give anhydrides.

\[
\text{CH}_3\text{CH}_2\text{C}—\text{Cl} + \text{Na}^+\overset{O}{—}\text{C—CH}_3 \rightarrow \text{CH}_3\text{CH}_2\text{C}—\overset{O}{—}\text{C—CH}_3 + \text{Na}^+\text{Cl}^- \quad (21.38)
\]

This is a second general method for the synthesis of anhydrides. Although the anhydride synthesis discussed in Sec. 20.9B can only be used for the synthesis of symmetrical anhydrides, the reactions of acid chlorides with carboxylate salts can be used to prepare mixed anhydrides, as the example in Eq. 21.38 illustrates.

**Summary: Use of Acid Chlorides in Organic Synthesis**

One of the most important general methods for converting a carboxylic acid into an ester, amide, or anhydride is first to convert the carboxylic acid into its acid chloride (Sec. 20.9A) and then use one of the acid chloride reactions discussed in this section to form the desired carboxylic acid derivative. To summarize:

\[
\text{R—C—OH} \xrightarrow{\text{SOCl}_2 \text{ or PCl}_5} \text{R—C—Cl} \quad (21.39)
\]

**B. Reactions of Anhydrides with Nucleophiles**

Anhydrides react with nucleophiles in much the same way as acid chlorides—that is, the reaction with an amine yields an amide, the reaction with an alcohol yields an ester, and so on.

\[
\text{CH}_3\text{O—NH}_2 + \text{H}_2\text{C—C—O—C—CH}_3 \rightarrow \text{acetic anhydride}
\]

\[
\text{CH}_3\text{O—NH—C—CH}_3 + \text{H}_2\text{C—C—OH} \quad (21.40)
\]

\[
\text{N—(p—methoxyphenyl)acetamide} \quad (75—79\% \text{ yield})
\]

\[
\text{CH}_3\text{O—C—CH}_3 + \text{H}_3\text{C—C—OH} \quad (21.41)
\]

\[
\text{2-acetoxybenzoic acid} \quad (80—90\% \text{ yield})
\]
Because most anhydrides are prepared from the corresponding carboxylic acids, the use of an anhydride to prepare an ester or amide wastes one equivalent of the parent acid as a leaving group. (For example, acetic acid is a by-product in Eqs. 21.40 and 21.41.) Therefore, this reaction in practice is used only with inexpensive and readily available anhydrides, such as acetic anhydride. However, one exception is the formation of half-esters and half-amides from cyclic anhydrides:

\[
\text{succinic anhydride} + \text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{O} = \text{C} - \text{C} = \text{OH} \quad \text{(21.42)}
\]

Half-amides of dicarboxylic acids are produced in analogous reactions of amines and cyclic anhydrides. These compounds can be cyclized to imides by treatment with dehydrating agents such as anhydrides, or, in some cases, just by heating, when 5- or 6-membered rings are formed. This reaction is the nitrogen analog of cyclic anhydride formation (Sec. 20.9B).

\[
\text{maleic anhydride} + \text{PhNH}_2 \rightarrow \text{C} = \text{NPh} \quad \text{(97% yield)}
\]

\[
(21.43)
\]

\[
\text{N-phenylmaleimide} \quad \text{(75–80% yield)}
\]

C. Reactions of Esters with Nucleophiles

Just as esters are much less reactive than acid chlorides toward hydrolysis, they are also much less reactive toward amines and alcohols. Nevertheless, reactions of esters with these nucleophiles are sometimes useful. The reaction of esters with ammonia or amines yields amides.

\[
\text{N} = \text{C} = \text{CH}_2 - \text{C} = \text{OC}_2\text{H}_5 + \text{NH}_3 \rightarrow \text{N} = \text{C} = \text{CH}_2 - \text{C} = \text{NH}_2 + \text{C}_2\text{H}_5\text{OH} \quad \text{(86% yield)}
\]

(21.44)

The reaction of esters with hydroxylamine (NH₂OH, Table 19.3) gives N-hydroxyamides; these compounds are known as hydroxamic acids.

\[
\text{R} - \text{C} = \text{OC}_2\text{H}_5 + \text{NH}_2\text{OH} \rightarrow \text{R} - \text{C} = \text{NHOH} + \text{C}_2\text{H}_5\text{OH} \quad \text{(21.45)}
\]

(Acid chlorides and anhydrides also react with hydroxylamine to form hydroxamic acids.) This chemistry is the basis of the hydroxamate test, used mostly for esters. The hydroxamic acid products are easily recognized because they form highly colored complexes with ferric ion.
When an ester reacts with an alcohol under acidic conditions, or with an alkoxide under basic conditions, a new ester is formed.

\[
\text{Ph} – C – OCH}_3 + \text{HO(CH}_2)_3\text{CH}_3 \xrightleftharpoons{K^+ \text{CH}_3\text{(CH}_2)_3\text{O}^-} \xrightarrow{\text{excess} \text{KOH}} \text{Ph} – C – O\text{(CH}_2)_3\text{CH}_3 + \text{CH}_3\text{OH} \quad (21.46)
\]

This reaction is an example of **transesterification**: the conversion of one ester into another by reaction with an alcohol. Transesterification typically has an equilibrium constant near unity, because neither ester is strongly favored at equilibrium. The reaction is driven to completion by the use of an excess of the displacing alcohol or by removal of a relatively volatile alcohol by-product as it is formed—Le Châtelier’s principle in action once again.

### PROBLEMS

21.15 Using an acid chloride synthesis as a first step, outline a conversion of hexanoic acid into each of the following compounds.

- (a) ethyl hexanoate
- (b) N-methylhexanamide

21.16 Complete the following reactions by giving the major organic products.

- (a) \(\text{CH}_3\text{CH}_2\text{CO}_2\text{H} \xrightarrow{\text{SOCl}_2, \text{(excess)}} \xrightarrow{\text{(CH}_3\text{)}_2\text{NH, (excess)}} \)
- (b) \(\xrightarrow{\text{pyridine, ether}} \)
- (c) \(\text{PhCH}_2 – C – Cl + \text{CH}_3\text{CH}_2\text{SH} \xrightarrow{} \)
- (d) \(\text{CH}_3\text{CH}_2\text{CH}_2 – C – Cl + \text{Na}^+ \xrightarrow{} \text{CH}_3 \)
- (e) \(\text{Cl} – C – Cl \xrightarrow{\text{(excess)}} + \text{CH}_3\text{OH} \xrightarrow{} \)
- (f) \(\text{Cl} – C – Cl + \text{CH}_3\text{OH (excess)} \xrightarrow{} \)
- (g) \(\text{C}_2\text{H}_5\text{O} – C – \text{OC}_2\text{H}_5 + \text{HO–CH}_2\text{CH}_2 – \text{OH} \xrightarrow{\text{acid catalyst, heat}} (\text{C}_3\text{H}_4\text{O}_3) \)
- (h) \(\xrightarrow{} \)

**PROBLEMS**
21.17 Give the structure of the product in the reaction of each of the following esters with isotopically labeled sodium hydroxide, Na\(^{18}\)OH. 

\[
\begin{align*}
\text{A:} & \quad \text{PhCH}_2\text{O} - \text{C} = \text{CH}_3 \\
\text{B:} & \quad \text{PhCH}_2\text{O} - \text{C} - \text{CH}_3
\end{align*}
\]

21.18 How would you synthesize each of the following compounds from an acid chloride?

(a) \[
\text{PhCH}_2\text{C} - \text{O} \quad \text{CH}_3
\]

(b) \[
\text{H}_3\text{C} - \text{O} - \text{C} - \text{NO}_2
\]

(c) \[
\text{C} = \text{O}
\]

(d) \[
\text{(CH}_3)_2\text{C} - \text{O} - \text{C} - \text{CH}_2 - \text{C} - \text{O} - \text{C(CH}_3)_3
\]

21.9 REDUCTION OF CARBOXYLIC ACID DERIVATIVES

A. Reduction of Esters to Primary Alcohols

Lithium aluminum hydride reduces all carboxylic acid derivatives. Reduction of esters with this reagent, like the reduction of carboxylic acids, gives primary alcohols.

\[
\begin{align*}
\text{ethyl 2-methylbutanoate} & \quad \text{LiAlH}_4 \quad \text{ether} \quad \text{H}_2\text{O}^+ \\
\text{2CH}_3\text{CH}_2\text{CH} - \text{C} - \text{OC}_2\text{H}_5 & \quad \text{2CH}_3\text{CH}_2\text{CH} - \text{CH}_2 - \text{OH} + \text{2CH}_2\text{OH} + \text{Li}^+, \text{Al}^{3+} \text{ salts} \\
\text{2-methyl-1-butanol} & \quad \text{ethanol}
\end{align*}
\]

Two alcohols are formed in this reaction, one derived from the acyl group of the ester (2-methyl-1-butanol in Eq. 21.47), and one derived from the alkoxy group (ethanol in Eq. 21.47). In most cases, a methyl or ethyl ester is used in this reaction, and the by-product methanol or ethanol is discarded; the alcohol derived from the acyl portion of the ester is typically the product of interest.

As noted several times (Sec. 20.10), the active nucleophile in LiAlH\(_4\) reductions is the hydride ion (H\(^-\)) delivered from \(^7\)AlH\(_4\), and this reduction is no exception. Hydride replaces alkoxy at the carbonyl group of the ester to give an aldehyde. (Write the mechanism of this reaction, another example of nucleophilic acyl substitution.)

\[
\begin{align*}
\text{Li}^+ \quad \text{AlH}_4^- + \text{R} - \text{C} - \text{OC}_2\text{H}_5 & \quad \text{R} - \text{C} - \text{H} + \text{Li}^+ \text{C}_2\text{H}_3\text{O}^- + \text{AlH}_3 \\
\text{an aldehyde}
\end{align*}
\]